Welcome!

• Please remove the Pre-activity Survey located at the front of your syllabus packet. Please fill it out and pass forward prior to the beginning of the lecture.

• It is important that you do this prior to the talk, as we will repeat these questions at the end of the program to gauge the effectiveness of the activity. These tests are not graded, but are used to build CME that suits your needs.

Your participation is greatly appreciated.

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Educational Objectives

At the conclusion of this activity, participants should be able to demonstrate the ability to:

• Select the most appropriate DMD therapies that can be used to initiate treatment earlier in the disease course

• Develop individualized treatment plans to optimize adherence and improve outcomes in patients with MS

• Describe how emerging biomarkers and newer MRI measures to improve the accuracy of diagnosis and monitoring of MS disease activity

Multiple Sclerosis: An Immuno-genetic Disease

Genetic Predisposition

Twins studies
-HLA-DR2 (OR11*1501) (antigen presentation)
-IL-2Ra (regulatory T-cells)
-IL-7Ra (memory T-cells)
-GWA5 (>100 alleles)

Environmental Factors

Demographics/Epidemics: Microbial Agents

EBV

Vitamin D

Smoking

Salt

Immune Dysregulation

MS

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Inflammation
Regeneration
Degeneration

Immunopathogenesis of MS
Inflammatory Processes Occurring Early in MS Lead to Demyelination and Axonal Loss

Time
Onset of Disease


McDonald Criteria: Dublin Revision 2011
• For DIS: At least one T2 lesion in two of the following locations:
  – Periventricular
  – Juxtacortical
  – Infratentorial
  – Spinal cord
• For DIT: Any new lesion on any follow-up scan after a baseline scan done anytime after onset of CIS

Single Early MRI
• In CIS, a single MRI, even in first 3 months, with Gad enhancing lesion(s) and T2H has high specificity for development of CDMS

CDMS = clinically definite MS

Radiologically Isolated Syndrome
5-year Risk for an Initial Clinical Event from a Multinational Cohort (RISC)
• Retrospective analysis of 20 databases from 5 countries
• >430 patients (largest cohort examined to date)
• 5-year observed conversion rate to first clinical event: 34%
• In multivariate model, several factors significantly associated with conversion:
  – Age (younger > older)
  – Gender (M > F)
  – Presence of spinal cord lesions

RISC = Radiologically Isolated Syndrome Consortium

RIS: Management Implications
• Potential for misdiagnosis
• High probability of benign MS
• “Wait and watch” approach may be best
• Future challenges:
  – How to identify high-risk RIS group
  – Standardized MRI
  – Combining MRI with other predictors
  – Population-based prospective study

“I look to the future because that’s where I’m going to spend the rest of my life.”
— George Burns

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Predicting the Course of MS

- Clinical features of onset bout
  - Motor worse than sensory
  - Polyregional worse than monosymptomatic
  - Early bladder involvement poor prognosis
- Incomplete recovery from initial attack
- Short interval between attacks

Assessing Risk

- Patients need to be informed and involved in decision-making process
- Need to steer patients to a limited number of options based upon disease severity
- Patient risk tolerance to adverse events
- Patient disease tolerance to neurologic dysfunction

Defining Breakthrough Disease

- 1 moderate/severe clinical relapse over 1 year
- 2 mild clinical relapses over 2 years
- 1-2 Gd enhancing brain lesions over 1 year
- 2 T2 lesions over 2 years
- A functionally significant worsening in cognition, ambulation, upper extremity function
- Need to account for time for medication to work optimally
- Follow-up MRI 6-12 months after treatment initiation

MRI and MS Prognosis

- Initial MRI
  - T2 lesion numbers
  - Median EDSS at 20 years = 6 for ≥10 T2 lesions
  - 3 or 4 Barkhof criteria moderate correlation with EDSS at 5 years

Existing and Emerging MS Therapies

*In March 2011, the FDA did not approve cladribine and requested Merck KGaA provide an improved understanding of its safety risks and overall benefit-risk profile.

Lawrence Peter “Yogi” Berra

“The future ain’t what it used to be.”
**ADVANCE**  
**Phase III Trial of PEGylated IFNb-1a in RRMS**

- PegIFN has longer t1/2 and results in prolonged exposure (AUC, Cmax) than standard formulations.
- Pts (n=1512) randomized to placebo, pegIFNb-1a 125 mcg q2wk, or q4wk.

**ENDPOINT** (reduction compared with placebo at 1 year)  
<table>
<thead>
<tr>
<th>Placebo</th>
<th>PegIFNb-1a Q2WK</th>
<th>PegIFNb-1a Q4WK</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>35.6%*</td>
<td>27.5%*</td>
</tr>
<tr>
<td>T2 lesions</td>
<td>67%*</td>
<td>28%*</td>
</tr>
<tr>
<td>Gd-enhancing T1 lesions</td>
<td>86%*</td>
<td>36%*</td>
</tr>
</tbody>
</table>

- Neutralizing Abs seen in <1% of patients in both IFN groups.
- Adverse events similar to known IFN profile (ISRs, pyrexia, flu-like symptoms, hepatic enzyme elevations).
- ATTAIN: long-term extension study from ADVANCE ongoing.

* Statistically significant finding.

PegIFN = polyethylene glycol interferon beta-1a; AUC = area under the curve; ARR = annualized relapse rate; IFN = interferon; Abs = antibodies; ISRs = injection site reactions.


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**Glatiramer Acetate Low-frequency Administration (GALA): Phase III Study**

**Primary Endpoint:** ARR 34.4% reduction, \( P < 0.0001 \)

<table>
<thead>
<tr>
<th>Placebo (( n = 441 ))</th>
<th>GA 40 mg tiw (( n = 884 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR ± SEM</td>
<td>0.592 ± 0.331</td>
</tr>
</tbody>
</table>

**Secondary Endpoint:** Cum. No. of New/Enlarging T2 Lesions

34.7% reduction, \( P < 0.0001 \)

<table>
<thead>
<tr>
<th>Placebo (( n = 461 ))</th>
<th>GA 40 mg tiw (( n = 943 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlarging T2 lesions</td>
<td>5.592 ± 3.65</td>
</tr>
</tbody>
</table>

ARR = annualized relapse rate; SEM = standard error of mean.


---

**Lymphocyte Trafficking Inhibition**  
*Implications for Multiple Sclerosis Therapy*

- Reduced leukocyte infiltration and brain inflammation.
- Leukocyte infiltration and brain inflammation.
- Leukocyte chemotactic signal.
- Blood vessel lumen.
- Leukocyte trafficking.
- Tissue VCAM-1.
- Blood vessels.
- Endothelial cells.
- Leukocyte chemoattractant signal.
- a4b1 (VLA-4).
- Neutrophil.

---

**Natalizumab v Placebo**  
**Affirm Study**

**Natalizumab**  
*Use in the Post-marketing Setting and PML Risk*

- 224,718 patient-years of natalizumab exposure.
- 324 patients have died (22%).

- Anti-JCV Antibody Status
  - Negative: 0.1/1,000
  - Positive: 0.1/1000

- Prior IS Use?
  - No: 95% CI: 0.0-0.35
  - Yes: 95% CI: 0.1-0.35

- Natalizumab exposure
  - 1-24 months: 0.7/1,000 patients
  - 25-48 months: 5.3/1,000 patients
  - 49-72 months: 6.1/1,000 patients
  - Insufficient data


---

**Estimated Incidence of Natalizumab-associated PML Stratified by Risk Factors**


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Anti-JCV Antibody Index Distribution in Anti-JCV Ab+ non-PML and pre-PML Patients with No Prior IS Use

PML Risk Estimates by Index Threshold in Anti-JCV Ab+ Patients with No Prior IS Use

Fingolimod (FTY720): Mode of Action

Managing Fingolimod Patients

• Prior to Treatment Initiation
  – Baseline CBC and hepatic panel
  – Ophthalmological examination
  – Cardiac status
  – Varicella immune status
  – Rx Initiation: 8-hour observation b/o bradycardia

• On Treatment
  – CBC, hepatic panel
  – Ophthalmological exam at 3-4 months
  – Check BP

Recent Additions to Fingolimod Prescribing Information

First Dosing Monitoring

Observe signs and symptoms of bradycardia for at least 8 hrs after first dose with hourly pulse and blood pressure measurement.

Obtain ECG prior to dosing and at the end of the observation period.

Monitor A/B block until normalization if heart rate >90 bpm, or a new slow 2nd-degree or higher.

If heart rate at least post-dose heart rate at the end of observation period should be monitored until heart rate increases.

Fingolimod (FTY720)

Prevents T cell invasion of CNS

FTY720 traps circulating lymphocytes in peripheral lymph nodes


EXPLORING THE LATEST ADVANCES IN MULTIPLE SCLEROSIS DIAGNOSIS AND MANAGEMENT

Teriflunomide
A Selective Dihydro-orotate Dehydrogenase Inhibitor

- A newly approved oral disease-modifier for relapsing forms of MS (RMS)
- Blocks de novo pyrimidine synthesis, reducing T- and B-cell proliferation and function in response to autoantigens
- Preserves replication and function of cells (e.g. haemopoietic cells, memory T-cells) living on the existing pyrimidine pool (salvage pathway)


Teriflunomide for RRMS (Phase III TEMSO Study)
Key Clinical Outcomes

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Placebo</th>
<th>Teriflunomide 7 mg</th>
<th>Teriflunomide 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR (primary endpoint)</td>
<td>&gt;24</td>
<td>22.3%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Reduction vs placebo</td>
<td>0.38*</td>
<td>0.31*</td>
<td></td>
</tr>
<tr>
<td>16-week confirmed disability progression</td>
<td>0.955</td>
<td>0.885*</td>
<td></td>
</tr>
<tr>
<td>Mean EDSS change (baseline to week 48)</td>
<td>0.089</td>
<td>0.042</td>
<td>-0.05*</td>
</tr>
</tbody>
</table>

*Statistically significant vs placebo.


Teriflunomide Counseling and Start-up

- Pregnancy Category X
- At Baseline: CBC with diff, LFTs, TB testing
- Monthly x 6 months: AST/ALT
- Every 6 months: CBC with diff, LFTs

Proposed Mechanisms: Dimethyl Fumarate

- An oral formulation of dimethyl fumarate
- Inhibits the expression of adhesion molecules and proinflammatory cytokines
- Induces a Th1 to Th2 shift
- Decreases circulating T cells
- Activates the Nrf2 pathway
- >30 years of use of fumaric acids in the treatment of psoriasis (both topical and oral)


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**DMF: Integrated Efficacy Analysis of DEFINE and CONFIRM**

<table>
<thead>
<tr>
<th>Endpoint (at 2 years)</th>
<th>Placebo (n = 771)</th>
<th>DMF BID (n = 769)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate (ARR)</td>
<td>0.37</td>
<td>0.19*</td>
</tr>
<tr>
<td>Reduction vs placebo</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients relapsed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR vs placebo</td>
<td>0.57*</td>
<td></td>
</tr>
<tr>
<td>Time to 12-week confirmed disability progression HR vs placebo</td>
<td>0.68*</td>
<td></td>
</tr>
<tr>
<td>Time to 24-week confirmed disability progression HR vs placebo</td>
<td>0.71*</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant vs placebo

**Alemtuzumab MOA**
- Targets CD52 antigen expressed on B and T lymphocytes
- FDA approved for leukemia
- Phase II study comparing Campath vs Rebif in 334 patients
  - 12 mg/day for 5 days at month 0, 12, 24
  - 24 mg/day for 5 days at month 0, 12, 24
- Three-year observation period with interim analyses

**Alemtuzumab vs Interferon-B1a: Care-MS Phase III Studies**

<table>
<thead>
<tr>
<th>CARE - MS1</th>
<th>CARE - MS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-B1a (12mg)</td>
<td>Alemtuzumab (12mg)</td>
</tr>
<tr>
<td>Arnl. relapse rate</td>
<td>0.39</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>54.9% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Sustained disability (%) pts</td>
<td>11</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>30% (P&lt;0.022)</td>
</tr>
<tr>
<td>Δ EDSS from baseline</td>
<td>-0.14</td>
</tr>
<tr>
<td>Net EDSS change</td>
<td>0.41 (P&lt;0.0001)</td>
</tr>
</tbody>
</table>


**Extension Analysis of Care-MS Phase III Studies**

<table>
<thead>
<tr>
<th>CARE-MS I</th>
<th>CARE-MS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>0.24</td>
</tr>
<tr>
<td>EDSS improvement</td>
<td>40%</td>
</tr>
<tr>
<td>Received alemtuzumab re-tx*</td>
<td>18%</td>
</tr>
</tbody>
</table>

*Criterion for re-treatment was 1 relapse or ≥2 new lesions on MRI
Fox E et al. Presented at AAN 2013; March 16-23, 2013; San Diego, CA; Abstract S41.001.

**Safety Analysis of Care-MS Phase III Studies**

**Autoimmune thyroid disorders**
- 19.4% in extension; 29.5% total study
- Autoimmune thyroiditis (ATD): 1.3%; myasthenia: 0.5% (n=3)

**Infections**
- More common with alemtuzumab compared with IFN
  - URTI, HIV, and fungal infections
  - No evidence that neutrophil or lymphocyte counts before a treatment course predicted infection risk

**Trials in Progressive MS**
- Secondary Progressive MS
  - ASCEND: Natalizumab vs Placebo
  - Siponimod vs Placebo
- Primary Progressive MS
  - FREEDOMS: Fingolimod vs Placebo
  - ORATORIO: Ocrelizumab vs Placebo
EXPLORING THE LATEST ADVANCES IN MULTIPLE SCLEROSIS DIAGNOSIS AND MANAGEMENT

Choice of Therapy

Aggressive Disease?

Yes

No

JOV AB Positive?

JOV AB Negative

Solist

Pregnancy?

Non-injection

NTZ

Fingo

DMF

NTZ

INSURANCE

Immunopathogenesis of MS

Defining Interferon ß Response Status in MS

• 15-year follow-up of pivotal MSCRG trial for weekly interferon
• 172 patients in placebo-controlled IFN-ß1a trial x 2 years
• In IFNb-1a group, disease activity predicted EDSS worsening:
  – Gadolinium-enhancing lesions (OR, 8.96; P<0.001)
  – Relapses (OR, 4.44; P=0.01)
  – New T2 lesions (OR, 2.90; P=0.08)
• Conclusion: New MRI activity during IFN-ß1a treatment correlates with suboptimal response

IFN-ß BIOMARKERS

MRI as a Surrogate of Future Disease Activity

• 370 patients underwent MRI at baseline and 1 year after beginning IFN
• Followed for relapse or disability progression in years 1-4
• At year 1: ≥1 Gd enhancing lesion or ≥2 T2 lesions had same risk for worsening disease in years 1-4 and for a clinical relapse within the first year
• MRI activity after starting IFN has similar implication as a relapse

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**Potential IFN-β Serum Biomarkers**

<table>
<thead>
<tr>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in IL-10</td>
<td>IL-17F levels&gt;200pg/ml</td>
</tr>
<tr>
<td>Reduction in Th1 cytokines</td>
<td>High baseline IFN-β levels</td>
</tr>
<tr>
<td>Increased in neurotrophic factors</td>
<td>NAB</td>
</tr>
<tr>
<td>Increased monocytes IFN-I secretion in response to TLR</td>
<td>Increase PSTAT1 and IFNR1 on monocytes at baseline</td>
</tr>
</tbody>
</table>

**Clinical Response to IFN-β**

**Key Points**
- Relapses are reduced by one-third
- Response is heterogeneous
- No validated laboratory biomarkers
- Persistent active MRI lesions at 6 mos predicts clinical activity
- Persistent high titer neutralizing Ab could be a reason to switch therapy

**Glatiramer Acetate Binds to HLA Class II on Antigen Presenting Cells and Induces Type-2 APCs**

**Response by Haplotype**

**DR and DQ Haplotypes Predictors of Clinical Response to GA**

<table>
<thead>
<tr>
<th>PROGNOSTIC PROFILE</th>
<th>HAPLOTYPES</th>
<th>NR / R (%R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognostic profile</td>
<td>DR15 - DQ6 absent DR17 - DQ2 present</td>
<td>10 / 2 (16.7%)</td>
</tr>
<tr>
<td>Neutral prognostic profile</td>
<td>DR15 - DQ6 present &amp; DR17 - DQ2 present</td>
<td>17 / 11 (39.5%)</td>
</tr>
<tr>
<td>Good prognostic profile</td>
<td>DR15 - DQ6 present &amp; DR17 - DQ2 absent</td>
<td>7 / 17 (70.8%)</td>
</tr>
</tbody>
</table>
EXPLORING THE LATEST ADVANCES IN MULTIPLE SCLEROSIS DIAGNOSIS AND MANAGEMENT

Summary of Potential GA-Biomarkers

<table>
<thead>
<tr>
<th>GA-RESPONDERS</th>
<th>GA NON-RESPONDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL4/IFNg</td>
<td>IL-18</td>
</tr>
<tr>
<td>IL-10</td>
<td>BDNF</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Caspase-3</td>
</tr>
<tr>
<td>FOXP3+</td>
<td>DQ2</td>
</tr>
<tr>
<td>DR15</td>
<td>DR17</td>
</tr>
</tbody>
</table>


Black Holes

NATALIZUMAB BIOMARKERS


BIOMARKERS OF Rx COMPLICATIONS

L-Selectin and Risk of PML in Natalizumab-treated MS Patients

EXPLORING THE LATEST ADVANCES IN MULTIPLE SCLEROSIS DIAGNOSIS AND MANAGEMENT

Serum IL-21 and Autoimmunity

Choosing Therapies—Biomarkers

- Antibodies to aquaporin-4
- Immune markers
  - IL-17 and response to IFN
  - Alemtuzumab autoimmunity: serum IL-21
  - Daclizumab: CD56^Bright
- Genetics/genomics (HLA): Response to GA
- Neutralizing antibodies (NAB) (IFN-B, natalizumab)
- JC virus exposure (natalizumab)

Future Issues

- Neuroprotection – how to recognize, measure, Rx
- Pathologic-based phenotyping will be increasingly important for treating progressive disease, informed (targeted) repair
- Biomarkers
- Measures of improvement

Patient Resource Tools

- The National Multiple Sclerosis Society
  - www.nmss.org
  - An online resource of patient information
- The American Academy of Neurology
  - http://patients.aan.com/patientbrochures
  - Understanding Multiple Sclerosis (located mid-page)
  - Available as a downloadable PDF or printed copies can be ordered by contacting Missy Render (mrender@aan.com)

Participant CME Evaluation

- Please remove the Post-activity Survey and Evaluation from the back of your packet
- If you are not seeking credit, we ask that you fill out the information pertaining to your degree and specialty, as well as the few questions in the Post-activity Survey measuring the knowledge and competence you have garnered from this program.
- In order to receive CME credit, please complete the Evaluation Form, as well, and return to onsite staff. Your participation will help shape future CME activities.

Thank You!